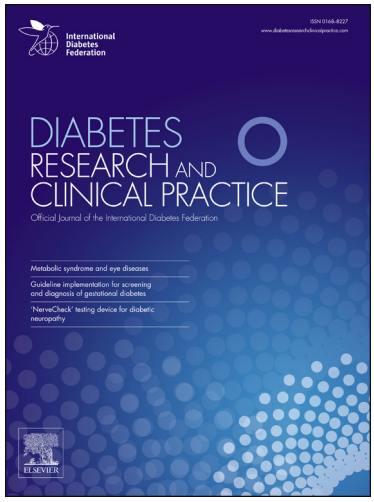

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Won Seon Jeon, Se Eun Park, Eun-Jung Rhee, Won-Young Lee, Ki-Won Oh, Sung-Woo Park, Cheol-Young Park

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Original Research Article

The association of serum glycated albumin with the prevalence of diabetic retinopathy in Korean patients with type 2 diabetes mellitus

Won Seon Jeon, Se Eun Park, Eun-Jung Rhee, Won-Young Lee,

Ki-Won Oh, Sung-Woo Park and Cheol-Young Park

Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Corresponding author:

Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108, Pyeong-dong, Jongno-gu, Seoul 110-746, Korea

Tel: +82-2-2001-1552; Fax: +82-2-2001-1588.

Email: cydoctor68@gmail.com

Running head: Serum glycated albumin and diabetic retinopathy

Abstract

Aims: To determine the clinical relationship between serum glycated albumin (GA) and diabetic retinopathy in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: A cross-sectional study including 424 patients with T2DM was conducted. Patients were divided into groups based on the presence of diabetic retinopathy and tertiles of serum GA and 1,5-anhydroglucitol levels.

Results: Patients in the highest tertile of GA had a higher risk of diabetic retinopathy than those in the lowest tertile. Further analysis divided the groups based on glycated hemoglobin (HbA1c) levels, either above or below 8% (64 mmol/mol), and revealed that in those with a HbA1c below 8% (64 mmol/mol), the higher GA subgroup had an increased presence of diabetic retinopathy.

Conclusions: An increased GA level was significantly correlated with the presence of diabetic retinopathy, and measuring GA levels in addition to HbA1c was beneficial as a marker for retinopathy, especially in patients with moderate glycemic control.

Keywords: type 2 diabetes mellitus, retinopathy, glycated albumin, HbA1c

1. Introduction

Diabetic retinopathy is a common microvascular complication of diabetes and a leading cause of visual disability in people of working age [1,2]. Many studies have investigated various risk factors for the onset and progression of diabetic retinopathy. The duration of diabetes, systolic blood pressure (SBP), and urinary albumin excretion have all been identified as major factors, but glycemic control is one of the most important risk factors [3,4].

Glycated hemoglobin (HbA1c) has traditionally been the standard marker of glycemic control and is also a measure for the risk of diabetic complications. Several studies have reported that a patient's mean HbA1c level is associated with the prediction of vascular complications, and achieving lower HbA1c levels by strict glycemic control impedes progression of complications, including retinopathy [5,6]. Therefore, glycemic control in patients with type 2 diabetes mellitus (T2DM) was confirmed as a very important factor for lowering a patient's risk for developing diabetic retinopathy.

However, it is also known that diabetic complications result from both sustained hyperglycemia and acute glucose fluctuations [7,8], and recent studies have suggested a role of glycemic variability or postprandial glucose excursion in diabetic micro- and macroangiopathy [9,10]. These reports indicate that even for the same HbA1c level, diabetic complications can occur at different rates depending upon the patient's glucose fluctuation status. Therefore, a special indicator for monitoring glucose fluctuations and excursions could have a potential role for helping to predict the development of diabetic complications.

Glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG) are markers that reflect glycemic variability [11,12]. GA has been reported to be a rapid indicator of glucose exposure over the previous two to four weeks, as the turnover of serum albumin is shorter than that for HbA1c [13]. Clinically, GA is recognized as an index that more strongly reflects postprandial glucose levels, which may possibly be a better predictor of retinopathy than the mean glucose level [11,14]. GA is also an early Amadori-type glycation product, which has been reported to play a role in atherogenesis by inducing inflammatory mediators in the vascular wall [13]. These results could suggest that GA is closely related to vascular complications that occur in patients with diabetes. The GA/HbA1c ratio is also a well-known marker for glycemic variability, and some studies have found that the GA/HbA1c ratio also correlates significantly with atherosclerosis [13,15,16].

Unlike GA, serum 1,5-AG has an inverse relationship with glycemic index as its renal reabsorption is competitively inhibited by glucose at elevated concentrations. As glucose concentrations surpass the renal

threshold, 1-5-AG is excreted in the urine, leading to a reduction in serum levels [17]. Additional caution is also needed when interpreting 1,5-AG under special clinical conditions, such as renal failure, elevated serum creatinine levels, or pregnancy. Furthermore, a meaningful difference of 1,5-AG levels was reported between genders [18]. Conversely, GA could be used in patients with renal failure, on dialysis treatment, or pregnancy [13].

Recent studies have found that predicting glycemic variability could differ depending on glucose status. For example, in well- or moderately-controlled patients with diabetes (i.e. HbA1c under 7.5 [58mmol/mol] or 8% [64 mmol/mol]), 1,5-AG or GA more strongly reflects glycemic excursion, as found in a study using a continuous glucose monitoring system (CGMS) [12,19,20].

The purpose of this study was to determine the clinical relationship between GA, GA/HbA1c, and 1,5-AG, which are markers of glycemic variability, and the presence of diabetic retinopathy. Furthermore, we tried to compare the performance of these markers of glycemic variability in predicting the presence of diabetic retinopathy in a moderately-controlled glycemic status.

2. Methods

2.1. Participants

A cross-sectional analysis was conducted in patients with T2DM that had been involved in the Seoul Metro City Diabetes Prevention Program (SMC-DPP) between August 2011 and February 2012.

The SMC-DPP was a community-based follow-up program that consisted of a pre-diabetes arm and a diabetes arm that recruited patients from public health centers in Seoul, Korea. In 2009, which was the baseline year, 700 patients with diabetes were enrolled in the SMC-DPP. This study analyzed the third-year study of SMC-DPP participants who had enrolled in 2009; 563 patients with diabetes were examined by the SMC-DPP between August 2011 and February 2012. We excluded 139 participants who had no record of fundoscopic imaging, non-diabetic ophthalmic lesions, unclear fundus readings, or insufficient laboratory data. Our final analysis included 424 patients with T2DM. We used a structured questionnaire to collect information on the participants' current smoking status, diabetes duration, and use of hypertensive medications. This study protocol was approved by the Institutional Review Board and the Ethics Committee of Kangbuk Samsung Hospital, and was carried out according to the principles of the Declaration of Helsinki. All participants provided written

informed consent before the study began.

2.2. Laboratory measurements

Serum GA levels were measured by an enzymatic method using an albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (LUCICA GA-L, Asahi Kasei Pharma Co., Tokyo, Japan) on an automated clinical immunology analyzer (Modular P800, Roche/Hitachi, Japan). The coefficients of variation for GA were 2.80-6.79% for the lower level and 1.59-2.95% for the higher level. GA (%) was calculated using the following formula: GA (%)=[(Glycoalbumin/total albumin)×100/1.14] + 2.9.[21] Serum 1,5-AG (Kyowa Medex, Tokyo, Japan) level was measured by an enzymatic colorimetric assay using an ADVIA 1800 Autoanalyzer (Bayer Diagnostics, Leverkusen, Germany). The coefficients of variation for 1,5-AG were 4.77-10.49% for the lower level and 4.01-8.94% for the higher level. HbA1c levels were measured by quantitative ion-exchange high-performance liquid chromatography using a Variant II Turbo (Bio-Rad Laboratories, Hercules, CA, USA). Glucose concentrations were obtained from a Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA, USA). Total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine levels were determined using enzymatic colorimetric assays (Siemens, Tarrytown, NY, USA). Serum insulin level was measured by an immunoradiometric assay (DIASource, Nivelles, Belgium). High-sensitivity C-reactive protein (hsCRP) levels were measured by a nephelometric assay using a BNII nephelometer (Dade Behring, Deerfield, IL, USA).

Blood samples were drawn for measurements of fasting plasma glucose, HbA1c, GA, 1,5-AG, fasting insulin, fasting c-peptide, hsCRP, total cholesterol, TG, HDL-C, and LDL-C after 12 hours of overnight fasting. The two-hour postprandial glucose levels were sampled after all patients had eaten the same meal (a sandwich and low fat milk: 490 kcal, 50% carbohydrate, 24% protein, 26% fat). Urine albumin excretion was assessed based on the ratio of urinary albumin to creatinine (A/C ratio). The glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) equation [22].

2.3. Retinal examinations

Fundal photography was performed after pupil dilatation. Five-field retinal photographs were taken of both eyes in all patients using a 45-degree digital retinal camera (TRC-NW6, Topcon, Tokyo, Japan). The five-field retinal photographs focused on the macular, upper nasal, upper temporal, lower nasal, and lower temporal areas. All photographs were interpreted by a retinal specialist using the Early Treatment Diabetic Retinopathy Study

(ETDRS) retinopathy severity scale [23]. Diabetic retinopathy was defined as present if any characteristic lesions were detected (i.e., a microaneurysm, cotton wool spot, intraretinal microvascular abnormality, haemorrhage, hard exudate, or new retinal vessel). In our analysis, patients were divided into two groups: those with or without diabetic retinopathy.

2.4. Statistical analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 18.0 (Chicago, IL, USA). For continuous variables, parameters that followed a normal distribution were analyzed with a t-test and described as the mean ± standard deviation (SD). The Chi-square test was used for binary variables to compare percentages across the diabetic retinopathy group. Variables with a skewed distribution were log-transformed for statistical analysis. The correlations between GA level and other parameters were assessed using Pearson's correlation analysis. Patients were divided into tertiles with respect to serum GA, GA/HbA1c and 1,5-AG levels. A multivariate logistic regression analysis was used to calculate the odds ratios or the presence of diabetic retinopathy. The predictive values of GA, HbA1c, and 1,5-AG for diabetic retinopathy were calculated by receiver-operating characteristic (ROC) curves. *P* -value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

This analysis included 424 patients with T2DM. Among all of the participants, 96 (22.5%) had been diagnosed with diabetic retinopathy. A comparison between the two groups (no diabetic retinopathy vs. diabetic retinopathy) revealed a significantly higher glucose level, HbA1c, GA level, GA/HbA1c ratio, urinary albumin excretion level, and diabetes duration in the retinopathy group. In addition, the body mass index (BMI), fasting insulin, fasting c-peptide, and 1,5-AG levels were significantly lower in the retinopathy group (Table 1).

3.2. Relationship between glycated albumin and various parameters

Serum GA levels were significantly correlated with HbA1c ($r = 0.811$, $p< 0.001$), 1,5-AG ($r = -0.686$, $p< 0.001$), postprandial glucose ($r = 0.677$, $p < 0.001$), fasting plasma glucose ($r = 0.558$, $p< 0.001$), urinary A/C ratio ($r =$

0.253, $p< 0.001$), fasting insulin (r = -0.195, $p< 0.001$), fasting c-peptide (r = -0.150, $p= 0.002$), hsCRP (r = 0.139, $p= 0.004$), and BMI (r = -0.132, $p= 0.007$) (Table 2).

3.3. Logistic regression analysis

Multivariate logistic regression analysis was performed to calculate the odds ratios (ORs) for the risk of diabetic retinopathy. Higher serum GA tertiles were significantly associated with an increased presence of diabetic retinopathy after adjusting for age and sex (p for trend <0.001). After adjusting for age, sex, GFR, fasting insulin, BMI, hsCRP, total cholesterol, SBP, current smoking status, diabetes duration, the use of hypertension medications, and HbA1c, the highest tertile of serum GA was significantly greater than the lowest tertile (OR 4.12, 95% confidence interval [CI]: 1.61-10.59, p = 0.003). We also analyzed the relationship between the GA/HbA1c ratio or 1,5-AG and diabetic retinopathy. In this analysis, the highest tertile of the GA/HbA1c ratio had an increased odds ratio of diabetic retinopathy compared to the lowest tertile (OR 2.94, 95% CI: 1.64-5.27, p < 0.001) after adjusting for age and sex. This significant association remained even after adjusting for GFR, fasting insulin, BMI, hsCRP, total cholesterol, SBP, current smoking, diabetes duration, and the use of hypertensive medications (p = 0.012). The OR for the participants with the lowest tertile of 1,5-AG was 3.85 (95% CI: 1.46-10.10), compared with the highest tertile of 1,5-AG after adjusting for multiple parameters (p = 0.006) (Table 3).

We divided our participants into two groups according to HbA1c category: HbA1c < 8% (64 mmol/mol) and HbA1c ≥ 8% (64 mmol/mol). In the HbA1c < 8% (64 mmol/mol) group, the prevalence of retinopathy was significant higher in the GA ≥50th percentile subgroup compared to the GA <50th percentile subgroup (27.4% vs. 10.3%, $p< 0.001$). The prevalence of retinopathy was also higher in the 1,5-AG <50th percentile subgroup than the 1,5-AG ≥50th percentile subgroup in the HbA1c < 8% (64 mmol/mol) group (27.6% vs. 10.3%, $p<$ 0.001). However, there was no significant difference in the prevalence of retinopathy according to binary GA levels or 1,5-AG levels in the HbA1c ≥ 8% (64 mmol/mol) group (data not shown).

We calculated ORs for diabetic retinopathy in two groups: HbA1c < 8% (64 mmol/mol) and HbA1c ≥ 8% (64 mmol/mol). In participants with an HbA1c below 8% (64 mmol/mol), the ORs for retinopathy were significantly higher in the GA ≥50th percentile subgroup than in the GA <50th percentile subgroup after adjusting for age, sex, GFR, BMI, hsCRP, total cholesterol, SBP, current smoking, diabetes duration, and the use of hypertensive medications (GA ≥50th percentile group: OR 2.11, 95% CI: 1.05-4.24, p= 0.035). The odds ratio of retinopathy in the 1,5-AG <50th percentile subgroup was significantly higher compared with the 1,5-AG

≥50th percentile subgroup in participants with a HbA1c less than 8% (64 mmol/mol). The odds ratio according to binary GA or 1,5-AG subgroup were not significantly different in the HbA1c ≥ 8% (64 mmol/mol) group (Table 4).

3.4. ROC curve for GA, HbA1c, and 1,5-AG for predicting diabetic retinopathy

To assess the ability to predict diabetic retinopathy, we analyzed the area under the ROC curve (AUC) for each glycemic marker. The AUC of GA was 0.74 (95% CI: 0.68-0.79, $p < 0.001$). The AUC of HbA1c was 0.70 (95% CI: 0.64-0.76, $p< 0.001$) and that of 1,5-AG was 0.69 (95% CI: 0.64-0.75, $p< 0.001$). In the HbA1c < 8% (64 mmol/mol) group, the AUC of GA (0.72, 95% CI: 0.66-0.79, $p< 0.001$) was larger than that of 1,5-AG (0.68, 95% CI: 0.61 to 0.75, $p< 0.001$). However, there was no statistically significant difference in the AUC between GA, HbA1c, and 1,5-AG as a whole as well as in the HbA1c < 8% (64 mmol/mol) subgroup.

4. Discussion

In the present study, we found that an increased GA level and GA/HbA1c ratio and a decreased 1,5-AG level were significantly associated with diabetic retinopathy in patients with T2DM. In particular, when we stratified the glycemic status according to binary GA or 1,5-AG levels in each HbA1c category, the results showed that a higher GA level and a lower 1,5-AG level were significantly associated with the presence of diabetic retinopathy in patients with moderately controlled diabetes.

Consistent with the findings of other studies, we observed a negative correlation of GA with fasting insulin, c-peptide, and BMI, and a positive correlation with hsCRP and the urinary A/C ratio [24-26]. With respect to the glycation index, we found a stronger correlation between GA and postprandial glucose levels than between GA and fasting plasma glucose levels.

Earlier studies have revealed that diabetic retinopathy was more closely related with postprandial glucose levels than HbA1c, and suggested that the detection of a marker reflecting postprandial glucose loading could play an important role in predicting diabetic complications [14,27]. Our results, as well as those of previous studies, have shown that GA has the ability to reflect postprandial glucose [28]. Furthermore, it is well known that GA is a precursor of advanced glycation end products (AGEs) [13]. Due to these characteristics, GA might be an independent factor of precipitating diabetic vascular complications[29,30]. In agreement with previous

reports, our findings showed that serum GA levels were significantly correlated with postprandial glucose levels and that postprandial glucose levels were significantly higher in the diabetic retinopathy group.

Glucose variability has been proposed as a contributor to the development or progression of diabetic complications, which includes not only macrovascular complication, but also microvascular complications such as diabetic retinopathy [30-32]. In 2009, Zoppini et al.[33] reported that the magnitude of hyperglycemia rather than fasting glucose variability predicted the development of diabetic retinopathy in patients with T2DM. However, since that study, most studies investigating glycemic variability and diabetic retinopathy in T2DM have found a positive association. Takao et al.[34,35] revealed that the risk of development of retinopathy was similar between those with poor glycemic control and low fasting glucose variability and those showing good control and high variability. Furthermore, they showed that fasting glucose variability was associated with the development of proliferative diabetic retinopathy as a severe form of retinopathy, independent of HbA1c. In the ADVANCE trial, Hirakawa et al.[36] found that fasting glucose and HbA1c variability were significantly associated with micro- and macrovascular events, and even more, all cause mortality. However, these studies all measured the standard deviation of fasting glucose as the glycemic variability marker. Further, the Takao study subjects included just 170 patients, although the follow-up period was lengthy. Some research groups have suggested that managing postprandial hyperglycemia is important in Asian patients for the reduction of glycemic variability [32,37]. Thus, we think that a simple tool to reflect glycemic variability, in particular, closely related with postprandial glucose levels, like GA or 1,5-AG, is useful for preventing or detecting diabetic retinopathy in Korean patients with T2DM.

Recent studies have found that predicting glycemic variability could differ depending on glucose status; 1,5-AG and GA have been shown to be useful markers for reflecting glycemic variability. Dungan et al.[19] reported that 1,5-AG more strongly reflects glycemic excursion than HbA1c in diabetic patients with HbA1c values between 6.5% (48 mmol/mol) and 8% (64 mmol/mol). Kim et al.[12] also reported that that 1,5-AG represented postprandial hyperglycemia only in well-controlled diabetic patients (HbA1c < 8% [64 mmol/mol]) using CGMS. Suh et al.[20] further confirmed that GA and 1,5-AG might be good indicators of glycemic variability, irrespective of the mean glucose level in patients with an HbA1c < 7.5% (58 mmol/mol).

Our study showed that the additional measurement of GA could help as a predictor for diabetic retinopathy in patients with HbA1c < 8% (64 mmol/mol). We also found that 1,5-AG had a close relationship with diabetic retinopathy and yielded additional benefits for patients with HbA1c values below 8% (64 mmol/mol), similar to our previous report on SMC-DPP in 2009 [38]. The reason why the additional GA or 1,5-AG measurement is

not useful in the relatively poor controlled state is unclear. However, we speculated that the relative contribution of glucose excursion could be different based on the overall glycemic controlled status. We assume that mean glucose level and glycemic variability would be important up to a specific point (i.e., below HbA1c 8%[64 mmol/mol]) but, in poorly-controlled states, sustained hyperglycemia itself has a larger impact on the development or progression of complications than do minor glucose fluctuations. Previously, Monnier et al.[39] suggested that the relative contributions of fasting and postprandial glucose differ according to the level of overall glycemic control. They reported that the relative contribution of postprandial glucose to overall glycemia decreases steadily with increasing HbA1c levels. GA and 1,5-AG appear to mainly reflect postprandial glucose levels. Judging from this viewpoint, we speculate that the impact of GA or 1,5-AG to predict complications would weaken with increasing HbA1c levels. In the case of 1,5-AG, Dungan[18] suggested that 1,5-AG could best reflect postprandial glucose in moderately controlled patients by HbA1c, as poorly controlled patients are prone to experience continuous glucosuria not just in the postprandial state. However, further studies are required to clarify this assumption.

The main characteristics of our study are as follows: First, the highest GA tertile was significantly related with the presence of diabetic retinopathy after adjusting for HbA1c as well as other risk factors. Second, GA or 1,5-AG had a similar predictive value for detecting diabetic retinopathy compared to HbA1c based on the results of the ROC analysis, although these markers did not show statistical superiority. Third, GA had the advantage of being an additional marker for predicting diabetic retinopathy in the clinical setting, in which HbA1c is the most commonly used tool to determine glycemic status. In other words, we suspect that GA could help narrow the range of patients at higher risk of diabetic retinopathy. In patients with HbA1c levels below 8% (64 mmol/mol), the ORs for diabetic retinopathy significantly increased in the higher GA subgroup. Based on our results, we believe that GA could be an additional marker for predicting diabetic retinopathy in patients with moderate glycemic control. Our study had several strengths. We stratified patients by their HbA1c levels (cut-off point HbA1c 8% (64 mmol/mol)) and studied the association of GA with diabetic retinopathy by HbA1c category. Furthermore, our study's results can be confirmed with an ongoing follow-up cohort study.

There were several limitations to the present study. Because this was a cross-sectional study, our results must be confirmed in our follow-up cohort study. Second, the serum GA and 1,5-AG samples were measured only at one visit. Third, we did not separately analyze participants according to the grade of diabetic retinopathy because the number of patients having severe retinopathy was too small. Despite these limitations, this study found that the presence of diabetic retinopathy appeared to be associated with serum GA, the GA/HbA1c ratio,

and 1,5-AG.

In conclusion, the present study indicated that there was an independent positive relationship between GA and diabetic retinopathy in Korean patients with T2DM. Our results suggest that the additional monitoring of GA along with HbA1c offers the benefit of predicting retinopathy, especially in Korean patients with moderately-controlled T2DM.

Conflict of Interests Statement

The authors declare no conflict of interest.

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Author contributions

W.S.J. analyzed and interpreted the data, contributed to discussion, and wrote the manuscript. C.Y.P. designed the study, analyzed and interpreted the data, and reviewed/edited the manuscript. S.E.P and E.J.R contributed to discussion and reviewed the manuscript. W.Y.L., K.W.O, and S.W.P. reviewed and edited the manuscript

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Table 1. Baseline characteristics of the study population according to the presence of diabetic retinopathy.

	No diabetic retinopathy (n = 328)	Diabetic retinopathy (n = 96)	*p*-value
Age (years)	56.55 ± 7.27	57.82±6.55	0.124
Sex (men/women, number)	185/143	58/38	0.484
Fasting plasma glucose (mmol/l)	7.55 ± 1.71	8.19 ± 2.33	0.014
Postprandial plasma glucose (mmol/l)	9.57 ± 2.82	10.78 ± 2.88	<0.001
HbA1c (%)	6.8 ± 1.0	7.6 ± 1.1	<0.001
Total cholesterol (mmol/l)	4.57 ± 0.93	4.47 ± 0.99	0.366
TG (mmol/l)	1.76 ± 1.36	1.76 ± 1.19	0.975
HDL-C (mmol/l)	1.35 ± 1.36	1.35 ± 0.28	0.976
LDL-C (mmol/l)	2.81 ± 0.88	2.72 ± 0.94	0.381
Fasting insulin (pmol/l)	64.36 ± 45.26	46.75 ± 30.98	<0.001
Fasting c-peptide (nmol/l)	0.97 ± 0.31	0.84 ± 0.35	<0.001
hsCRP (nmol/l)	1.00 ± 1.80	1.13 ± 1.48	0.541
BMI (kg/m^2)	25.01 ± 3.22	24.09 ± 2.88	0.013
Systolic blood pressure (mmHg)	132.67 ± 15.48	132.29 ± 15.28	0.835
Diastolic blood pressure (mmHg)	76.59 ± 10.04	76.32 ± 9.34	0.822
GFR	107.28 ± 24.26	105.98 ± 25.23	0.558
Urinary A/C ratio (mg/g)	28.63 ± 56.02	49.09 ± 93.00	<0.001
Current smoker (%)	49 (15.0%)	12 (12.6%)	0.566
Taking HTN medication (%)	146 (44.8%)	44 (45.8%)	0.856
Diabetes duration (years)	6.28 ± 4.29	12.31 ± 6.87	<0.001
GA (%)	17.15 ± 3.46	20.21 ± 4.29	<0.001
GA/HbA1c ratio	2.51 ± 0.30	2.67 ± 0.31	<0.001
1,5-AG (μg/mL)	13.69 ± 8.14	8.64 ± 6.51	<0.001

TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; BMI: body mass index; GFR: glomerular filtration rate; A/C ratio: albumin to creatinine ratio; HTN: hypertension; GA: glycated albumin; 1,5-AG: 1,5-anhydroglucitol

Data are expressed as the mean±SD or frequency (%).

Table 2. Correlations between glycated albumin (GA) [a] and clinical parameters.

	r	*p*-value
Age	0.058	0.232
Fasting plasma glucose	0.558	<0.001*
Postprandial glucose	0.677	<0.001*
HbA1c	0.811	<0.001*
Total cholesterol	-0.001	0.982
TG[a]	-0.004	0.937
HDL-C	-0.037	0.451
LDL-C	-0.025	0.612
Fasting insulin[a]	-0.195	<0.001*
C-peptide	-0.150	0.002*
hsCRP[a]	0.139	0.004*
BMI	-0.132	0.007*
Systolic blood pressure	-0.083	0.098
Diastolic blood pressure	-0.067	0.185
Urinary A/C ratio[a]	0.253	<0.001*
GA/HbA1c ratio[a]	0.687	<0.001*
1,5-AG[a]	-0.686	<0.001*

TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; BMI: body mass index; A/C ratio: albumin to creatinine ratio; 1,5-AG: 1,5-anhydroglucitol

*p-value <0.05 was considered statistically significant.

[a]Logarithmic transformation was performed due to a skewed distribution.

Table 3. Multivariable logistic regression analysis showing odds ratios for diabetic retinopathy according to GA, GA/HbA1c, and 1,5-AG tertiles.

	Model 1		Model 2		Model 3	
	Odds ratio	*p*-value	Odds ratio	*p*-value	Odds ratio	*p*-value
GA						
Tertile-1 (<15.85%, n = 141)	1 (reference)		1 (reference)		1 (reference)	
Tertile-2 (15.85-18.67%, n = 142)	2.02 (0.96-4.25)	0.066	1.93 (0.91-4.09)	0.084	1.32 (0.57-3.09)	0.519
Tertile-3 (>18.67%, n = 141)	8.06 (4.08-15.93)	<0.001	7.69 (3.86-15.30)	<0.001	4.12 (1.61-10.59)	0.003
p for trend	<0.001		<0.001		0.002	
GA/HbA1c ratio						
Tertile-1 (<2.40, n = 142)	1 (reference)		1 (reference)		1 (reference)	
Tertile-2 (2.40-2.63, n = 141)	1.29 (0.69-2.43)	0.426	1.23 (0.65-2.32)	0.531	1.57 (0.75-3.30)	0.234
Tertile-3 (>2.63, n = 141)	2.94 (1.64-5.27)	<0.001	2.61 (1.41-4.81)	0.002	2.56 (1.23-5.33)	0.012
p for trend	<0.001		0.001		0.011	
1,5-AG [a]						
Tertile-1 (<7.9 μg/mL, n = 139)	8.53 (4.06-17.89)	<0.001	8.66 (4.10-18.28)	<0.001	3.85 (1.46-10.10)	0.006
Tertile-2 (7.9-15.7μg/mL, n = 141)	4.36 (2.05-9.26)	<0.001	4.35 (2.04-9.27)	<0.001	2.70 (1.16-6.33)	0.022
Tertile-3 (>15.7 μg/mL, n = 142)	1 (reference)		1 (reference)		1 (reference)	
p for trend	<0.001		<0.001		0.007	

GA: glycated albumin; 1,5-AG: 1,5-anhydroglucitol.

Model 1: Adjusted for age, sex.

Model 2: Adjusted for age, sex, GFR, BMI, and hsCRP.

Model 3: Model 2 further adjusted for HbA1c, total cholesterol, SBP, current smoking, duration of diabetes, and the use of hypertensive medications (GA/HbA1c ratio: not including HbA1c).

[a]1,5-AG was analyzed in 422 patients due to missing data in two patients.

Table 4- Multivariable logistic regression analysis showing odds ratios for diabetic retinopathy according to HbA1c category.

Category	Odds ratio		*p*-value
	GA <50th percentile	GA ≥50th percentile	
HbA1c < 8.0% (64mmol/mol)[a] (n = 350)	1	2.11 (1.05-4.24)	0.035
HbA1c ≥ 8.0% (64mmol/mol)[b] (n = 74)	1	1.49 (0.44-5.10)	0.522
	1.5-AG <50th percentile	1.5-AG ≥50th percentile	
HbA1c < 8.0% (64mmol/mol)[a] (n = 350)	2.74 (1.37-5.50)	1	0.005
HbA1c ≥ 8.0% (64mmol/mol)[b] (n = 74)	0.79 (0.22-2.88)	1	0.720

Adjusted for age, sex, GFR, BMI, hsCRP, total cholesterol, SBP, smoking status, duration of diabetes, and the use of hypertensive medications.

[a]In the HbA1c < 8.0% (64 mmol/mol) group, the cut-off value of the 50th percentile GA was 16.34% and that of 1,5-AG was 13.6 μg/mL.

[b]In the HbA1c ≥8.0% (64 mmol/mol) group, the cut-off value of the 50th percentile GA was 22.38% and that of 1,5-AG was 3.1 μg/mL.

Highlights

This study finds that an increased serum glycated albumin level is significantly related with the presence of diabetic retinopathy, and the measurement of glycated albumin in addition to HbA1c could be beneficial as a predictor for diabetic retinopathy, especially in patients with moderately controlled type 2 diabetes.

These results indicate that the measurement of another glycemic variability marker have the advantage of being an additional marker of prediction of diabetic retinopathy in the clinical setting that HbA1c is commonly used tool to determine glycemic status.